CofC

Docket No. 17008CONDIV5CON3(AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

In Re Application of:
Burk

U.S. Patent No. 6,716,876 B2

Issued: April 6, 2004

For: CYCLOPENTANE(ENE) HEPTENOIC OR HEPTANOIC ACID AND DERIVATIVES THEREOF USEFUL AS THERAPEUTIC AGENTS

Commisioner of Patents
Alexandria, VA 22313

REQUEST FOR
CERTIFICATE OF CORRECTION
UNDER RULE 322 (OFFICE MISTAKE)

Dear Sir:

Please correct the above-identified patent as shown on the accompanying Certificate of Correction Form PTO-1050.

These corrections are requested for the following reasons:

IN THE SPECIFICATION:

Column 2, line 31 (page 3, line 4); delete "C5" and insert in place thereof --C_5--
Column 2, line 51 (page 3, line 23); delete "use-" and insert in place thereof
--use--
Column 6, line 17 (page 9, line 24); delete "27b" and insert in place thereof --17b--
Column 6, line 52 (page 10, line 37); delete "2β" and insert in place thereof -- -2β --
Column 6, line 62 (page 11, line 10); delete "3α5α" and insert in place thereof --3α, 5α--
Column 6, line 64 (page 11, line 13); delete "3α5α" and insert in place thereof --3α,5α--
Column 9, line 49 (page 17, line 3); delete "3αethoxy" and insert in place thereof --3α-ethoxy--
Column 10, line 2 (page 17, line 26); delete "2β" and insert in place thereof --2β- --
Column 10, line 22 (page 18, line 8); delete "5" and insert in place thereof --5α--

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Column 10, line 49 (page 19, line 3); delete "2β" and insert in place thereof --2β- --

Column 11, line 2 (page 19, line 28); delete "1E" and insert in place thereof --1E- --

Column 11, line 28 (page 20, lines 16-17); delete "alp"

Column 13, line 5 (page 24, line 12); delete "1-E" and insert in place thereof --1E--

Column 14, line 3 (page 26, line 11); delete "(methoxy" and insert in place thereof --methoxy--

Column 17, line 25 (page 33, line 11); delete "2β" and insert in place thereof --2β- --

Column 17, line 26 (page 33, line 11); delete "octenyl" and insert in place thereof --octenyl)--

Column 17, line 56 (page 34, line 4); delete "add" and insert in place thereof --acid--

Please send the Certificate to:

Allergan, Inc.
ROBERT J. BARAN (T2-7H)
Intellectual Property Dept.
2525 Dupont Drive
Irvine, CA 92612

No fee is thought to be due, but if we are incorrect, please use our deposit account 01-0885 for fees related to this request.

Respectfully Submitted,

RJ Baran

Robert J. Baran
Registration No. 25,806
Telephone: 714/246-4669
Telecopier: 714/246-4249

Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612

CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST-CLASS MAIL WITH SUFFICIENT POSTAGE IN AN ENVELOPE ADDRESSED TO: MAIL STOP CERTIFICATE OF CORRECTION-NON FEE; COMMISSIONER OF PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450 ON 5/26/2004 Printed Name of Person Making Deposit: Bonnie Ferguson; Signature of Person Making Deposit; Bonnie Ferguson Date: 5/26/2004

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO: 6,716,876 B2

DATED: April 6, 2004

INVENTORS: Burk

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

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Column 2

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Column 6

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Line 52; delete "2β" and insert in place thereof -- -2β --

Line 62; delete "3α5α" and insert in place thereof --3α, 5α--

Line 64; delete "3α5α" and insert in place thereof --3α,5α--

Column 9, line 49; delete "3αethoxy" and insert in place thereof --3α-ethoxy--

Column 10

Line 2; delete "2β" and insert in place thereof --2β- --

Line 22 ; delete "5" and insert in place thereof --5α--

Line 49; delete "2β" and insert in place thereof --2β- --

MAILING ADDRESS OF SENDER: Robert J. Baran (T2-7H)
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612

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Column 17

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Line 26; delete "octenyl" and insert in place thereof --octenyl)--

Line 56; delete "add" and insert in place thereof --acid--

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FORM PTO 1050

CYCLOPENTANE(ENE)HEPTENOIC OR HEPTANOIC ACIDS AND DERIVATIVES THEREOF USEFUL AS THERAPEUTIC AGENTS

This patent application is a continuation of U.S. Ser. No. 09/919,318 filed Jul. 31, 2001 which is a continuation of U.S. Ser. No. 09/448,082 which was filed on Nov. 23, 1999, now U.S. Pat. No. 6,303,658, which is a continuation of U.S. Ser. No. 09/225,034, which was filed on Jan. 4, 1999, now U.S. Pat. No. 5,990,138, issued on Nov. 23, 1999; which is a divisional of U.S. Ser. No. 09/084,805, filed May 26, 1998, now U.S. Pat. No. 5,906,989, issued on May 25, 1999; which is a divisional of U.S. Ser. No. 08/861,414, which was filed on May 21, 1997, now U.S. Pat. No. 5,798,378, issued on Aug. 25, 1998; which is a divisional of U.S. Ser. No. 08/740,883, filed Nov. 4, 1996, now U.S. Pat. No. 5,681,848, issued Oct. 28, 1997; which is a divisional of U.S. Ser. No. 08/445,842 which was filed on Jul. 11, 1995, now U.S. Pat. No. 5,587,391, issued Dec. 4, 1996; which is a divisional of U.S. Ser. No. 08/174, 535, which was filed on Dec. 28, 1993, now U.S. Pat. No. 5,545,665, issued Aug. 13, 1996.

The present invention provides 7-[5-hydroxy-2-(hydroxy-hydrocarbyl or heteroatom-substituted hydroxyhydrocarbyl)-3-hydroxycyclopentyl(enyl)] heptanoic or heptenoic acids and amine, amide, ether, ester and alcohol derivatives of said acids, wherein one or more of said hydroxy groups are replaced by an ether group. The compounds of this invention are potent ocular hypotensives, and are particularly suitable for the management of glaucoma. Moreover, the compounds of this invention are smooth muscle relaxants with broad application in systemic hypertensive and pulmonary diseases; with additional application in gastrointestinal disease, reproduction, fertility, incontinence, shock, inflammation, immune regulation, disorders of bone metabolism, renal dysfunction, cancer and other hypoproliferative diseases.

BACKGROUND OF THE INVENTION

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical β-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Prostaglandins were earlier regarded as potent ocular hypertensives, however, evidence accumulated in the last two decades shows that some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of glaucoma. (See, for example, Starr, M. S. *Exp. Eye Res.* 1971, 11, pp. 170–177; Bito, L. Z. *Biological Protection with Prostaglandins* Cohen, M. M., ed., Boca Raton, Fla., CRC Press Inc., 1985, pp. 231–252; and Bito, L. Z., *Applied Pharmacology in the Medical Treatment of Glaucomas* Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477–505). Such prostaglandins include $PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_2, and certain lipid-soluble esters, such as C_1 to C_5 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

In the U.S. Pat. No. 4,599,353 certain prostaglandins, in particular PGE_2 and $PGF_{2\alpha}$ and the C_1 to C5 alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management. C5

Although the precise mechanism is not yet known, recent experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et al., *Invest. Ophthalmol. Vis. Sci.* 28 (suppl), 284 (1987)].

The isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compound, which was attributed to its more effective penetration through the cornea. In 1987 this compound was described as "the most potent ocular hypotensive agent ever reported." [See, for example, Bito, L. Z., *Arch. Ophthalmol,* 105, 1036 (1987); and Siebold et al., *Prodrug* 5, 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular $PGF_{2\alpha}$ and its prodrugs, e.g. its 1-isopropyl ester, in humans. The clinical potential of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma, is greatly limited by these side effects. use

Certain phenyl and phenoxy mono, tri and tetra nor prostaglandins and their 1-esters are disclosed in European Patent Application 0,364,417 as useful in the treatment of glaucoma or ocular hypertension.

In a series of copending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending U.S. Ser. No. 386,835 (filed Jul. 27, 1989), relates to certain 1,1-acyl-prostaglandins, such as 11-pivaloyl 11-acetyl, 11-isobutyryl, 11-valeryl, and

soluble esters, such as C_1 to C_5 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

In the United States Patent No. 4,599,353 certain prostaglandins, in particular PGE_2 and $PGF_{2\alpha}$ and the C_1 to C_5 alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management.

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Certain phenyl and phenoxy mono, tri and tetra nor prostaglandins and their 1-esters are disclosed in European Patent Application 0,364,417 as useful in the treatment of glaucoma or ocular hypertension.

In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending USSN 386,835 (filed 27 July 1989), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl 11-

FIG. 3 is a schematic representation of the synthesis of 15-acyl analogues of certain of the ethers of the invention.

FIG. 4 is a schematic representation of the synthesis of certain of the 5, 6 trans compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

In all of the above formulae the dotted lines on bonds between carbons 5 and 6 (C-5) of the a chain, between carbons 13 and 14 (C-13) of the w chain, and between carbons 10 and 11 (C-11) of the cyclopentane ring, indicate a single or a double bond which can be in the cis or trans configuration (Of course, the C-10 and C-11 double bonds being part of the cyclopentane ring will exist only as, cis double bonds). If two solid lines are used that indicates a specific configuration for that double bond. Hatched lines at positions C-8, C-9, C-11, C-12 and C-15 indicate the a configuration. If one were to draw the b configuration, a solid triangular line would be used.

In the compounds used in accordance with the present invention, compounds having the C-8, C-9, C-11, C-12 or C-15 substituents in the a or b configuration are contemplated.

For the purpose of this invention, unless further limited, the term "alkyl" refers to alkyl groups having from one to ten carbon atoms, the term "cycloalkyl" refers to cycloalkyl groups having from three to seven carbon atoms, the term "aryl" refers to aryl groups having from four to ten carbon atoms. The term "hydrocarbyl" means radicals having up to 20 carbon atoms and the remaining atoms comprising said hydrocarbyl radical are hydrogen. In the "heteroatom-substituted" radicals any of the carbon atoms or the hydrogen atoms may be replaced by one of the above defined heteroatoms. Such hydrocarbyl radicals include aryl, alkyl, alkenyl and alkynyl groups of appropriate lengths, and may be methyl, ethyl, propyl, butyl, pentyl, or hexyl, or an isomeric form thereof; ethenyl, propenyl, etc.; phenyl, etc.

In FIG. 1 PGF $_{2\alpha}$ or 17-phenyl (18, 19, 20 trinor) $PGF_{2\alpha}$ is reacted with diazomethane to convert such compounds to the corresponding 1-methyl ester. In this scheme R_4 is n-propyl or phenyl. Subsequently, as shown in Reaction 1b and further illustrated in Examples 1 and 3, the above 1-methyl esters are reacted with an organoiodide, represented by R_1I, R_2I or R_3I, in the presence of Ag_2O and dimethyl formamide, e.g. at 23° C.

In FIG. 2 the 1-methyl ester, prepared according to the reaction 1b of FIG. 1, is reacted to provide various compounds of this invention. As shown in Reaction 2d and Example 7, the 1-methyl ester may be hydrolyzed with 0.5 N aqueous LiOH in tetrahydrofuran (THF) to yield the corresponding acid. Alternatively, the 1-methylester may be reduced with $LiBH_4$ in ethylether, in accordance with Reaction 2c and as illustrated in Example 6, to yield the corresponding alcohol. This alcohol may be subsequently converted into the 5-t-butyl dimethyl siloxy derivative and reacted, in accordance with Reaction 2e, with 2,6-di-t-butyl pyridine in CH_2Cl_2 and subsequently reacted with methyl triflate (MeOTF) to form the 1-methoxy derivative. To provide other 1-hydrocarbyloxy esters the alternate Reaction 2e may be utilized whereby the 1-alcohol may be reacted with the hydrocarbyl chloride, R_7Cl, wherein R_7 is a hydrocarbyl radical comprising up to 20 carbon atoms, e.g. a C1 to C4 alkyl chloride, in the presence 4-dimethylaminopyridine (DMAP) in triethylamine and CH_2Cl_2. Finally, the 1-methylester may be reacted, in accordance with Reaction 2a and as illustrated in Example 4, with an amine, R_5R_6NH, wherein R_5 and R_6 are selected from the group consisting of hydrogen and hydrocarbyl radicals, preferably hydrogen and C_1 to C_4 alkyl radicals, in CH_3OH, for example at a temperature of 55° C., to yield the corresponding amides. Such amides may be subsequently reduced with $LiAlH_4$ in THF, in accordance with Reaction 2b and as illustrated by Example 5, to yield the corresponding amines.

In FIG. 3 the 1-methyl ester, prepared according to the reaction scheme of FIG. 1, is reacted in accordance with Reaction 3a of FIG. 3 and as illustrated by Example 17 to yield the 15-pivaloyl ester of said 1-methyl ester. The compound is subsequently reacted in accordance with Reaction 3b of FIG. 3 and as illustrated by Example 17a to yield the 11-methoxy derivative. This compound may then be converted to the 1-acid in accordance with Reaction 3c, as illustrated by Example 27b to yield the 11-methoxy, 15 pivaloyloxy acid of the invention. 17b

In FIG. 4, the 1-methylester prepared in accordance with the reaction scheme of FIG. 1, is consecutively reacted according to Reactions 1a through 1c, as illustrated in Example 18 to yield the 5-trans compounds of this invention.

The following novel compounds may be used in the pharmaceutical compositions and the methods of treatment of the present invention.

Methyl 7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenoate

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenoic acid

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cylopentyl]-5Z-hepten-1-ol

7-[5α-Hydroxy-2β-(3α-pivalyl-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenoic acid

Methyl 7-[5α-Hydroxy-2β-(3α-pivalyl-1E-octenyl)3α-methoxy-cyclopentyl]-5Z-heptenoate

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-hepten-1-pivalate

Methyl 7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5E-heptenoate

7-(5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5E-heptenoic acid

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5E-hepten-1-ol

Methyl 7-[3α-ethoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenoate

7-[3α-Ethoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenoic acid

7-[3α-Ethoxy-5α-hydroxy 2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-hepten-1-ol

7-[5α-Hydroxy 2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide −2/3

N,N-Dimethyl-7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide

Methyl 7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-(2-propenoxy)-cyclopentyl]-5Z-heptenoate

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-(2-propenoxy)-cyclopentyl]-5Z-hepten-1-ol

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-(2-propenoxy)-cyclopentyl]-5Z-heptenoic acid

Methyl 7-[3α5α-dimethoxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenoate 3α, 5α

7-[3α5α-dimethoxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenoic acid 3α, 5α

7-[3α,5α-dimethoxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-hepten-1-ol

in accordance with Reaction 2e, with 2,6-di-t-butyl pyridine in CH_2Cl_2 and subsequently reacted with methyl triflate (MeOTF) to form the 1-methoxy derivative. To provide other 1-hydrocarbyloxy esters the alternate Reaction 2e may be utilized whereby the 1-alcohol may be reacted with the hydrocarbyl chloride, R_7Cl, wherein R_7 is a hydrocarbyl radical comprising up to 20 carbon atoms, e.g. a C1 to C4 alkyl chloride, in the presence 4-dimethylaminopyridine (DMAP) in triethylamine and CH_2Cl_2. Finally, the 1-methylester may be reacted, in accordance with Reaction 2a and as illustrated in Example 4, with an amine, R_5R_6NH, wherein R_5 and R_6 are selected from the group consisting of hydrogen and hydrocarbyl radicals, preferably hydrogen and C_1 to C_4 alkyl radicals, in CH_3OH, for example at a temperature of 55°C, to yield the corresponding amides. Such amides may be subsequently reduced with $LiAlH_4$ in THF, in accordance with Reaction 2b and as illustrated by Example 5, to yield the corresponding amines.

In Figure 3 the 1-methyl ester, prepared according to the reaction scheme of Figure 1, is reacted in accordance with Reaction 3a of Figure 3 and as illustrated by Example 17 to yield the 15-pivaloyl ester of said 1-methyl ester. The compound is subsequently reacted in accordance with Reaction 3b of Figure 3 and as illustrated by Example 17a to yield the 11-methoxy derivative. This compound may then be converted to the 1-acid in accordance with Reaction 3c, as illustrated by Example 17b, to yield the 11-methoxy, 15 pivaloyloxy acid of the invention.

In Figure 4, the 1-methylester prepared in accordance with the reaction scheme of Figure 1, is consecutively reacted according to Reactions 1a through 1c, as illustrated in Example 18 to yield the 5-trans compounds of this invention.

The following novel compounds may be used in the pharmaceutical compositions and the methods of treatment of the present invention.

Methyl 7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenoate

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenoic acid

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-hepten-1-ol

7-[5α-Hydroxy-2β-(3α-pivalyl-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenoic acid

Methyl 7-[5α-Hydroxy-2β-(3α-pivalyl-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenoate

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-hepten-1-pivalate

Methyl 7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5E-heptenoate

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5E-heptenoic acid

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5E-hepten-1-ol

Methyl 7-[3α-ethoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenoate

7-[3α-Ethoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenoic acid

7-[3α-Ethoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-hepten-1-ol

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide X

N,N-Dimethyl-7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide

Methyl 7-[5α-hydroxy-2β-(3α–hydroxy-1E-octenyl)-3α-(2-propenoxy)-cyclopentyl]-5Z-heptenoate

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-(2-propenoxy)-cyclopentyl]-5Z-hepten-1-ol

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-(2-propenoxy)-cyclopentyl]-5Z-heptenoic acid

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7-[3α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-5α-methoxy-cyclopentyl]-5Z-hepten-1-ol

N-Isopropyl-7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide

N-Isopropyl-7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamine

N,N-Dimethyl-7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy- cyclopentyl]-5Z-heptenamine

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-propoxy-cyclopentyl]-5Z-hepten-1-ol

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-propoxy-cyclopentyl]-5Z-heptenoic acid

EXAMPLE 4d

N,N-Dimethyl-7-(5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide

Dimethylamine (~5 ml) was condensed in a tube containing 100 mg (0.1639 mmol) of the 5-t-butyldimethylsiloxy, 3-methoxy derivative of $PGE_{2\alpha}$, methylester dissolved in 6.0 mL of CH_3OH. The resultant solution was stirred in a sealed glass tube for 48 hours and concentrated in vacuo. The residue diluted with THF (1.0 mL) and treated with Bu_4NF (0.26 mL of a 1.0M solution, 0.262 mmol) at 23° C. After 16 hours, the reaction was diluted with Et_2O and washed with H_2O. The organic portion was dried ($MgSO_4$), filtered and concentrated in vacuo. FCC (100% EtOAc followed by 9:1 CH_2Cl_2/MeOH) gave 24.2 mg. (39%) of the product.

EXAMPLE 5

N-Isopropyl-7-(5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamine

In accordance with Reaction 2b of FIG. 2, 75mg of the compound of Example 4, dissolved in 2.0 mL of tetrahydrofuran (THF) were treated with 34.6 mg. (0.9165. mmol) of lithium aluminumhydride (LAH) at 23° C. After 24 hours, the reaction mixture was quenched with 2.0 N NaOH and extracted with EtOAc. The organic layer was dried over anhydrous MgSO4, filtered and alp concentrated under vacuum. The residue was purified with FCC using a 6:1:0.1 mixture of CH_2Cl_2/MeOH/NH4OH to yield 19.0 mg. (26% yield)of the named compound.

EXAMPLE 5a

N,N-Dimethyl-7-(5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamine

The named compound is prepared by substitution of the compound of Example 4a in the procedure of Example 5.

EXAMPLE 6

7-(5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-hepten-1-ol

In accordance with Reaction 2c of FIG. 2, 20.2 mg (0.0529 mmol) of the compound of Example 1 were dissolved in 1.5 mL of Et_2O and treated with 2.3 mg (0.105 mmol) of $LiBH_4$ to yield a reaction mixture comprising the named product. The resulting product was purified by FCC with a 1 to 1 mixture of hex/EtOAc followed by 100% EtOAc to yield 16.3 mg. (87%) of the named compound.

EXAMPLE 6a

7-[3α-Ethoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-hepten-1-ol

The named compound is prepared by substituting the compound of Example 1b in the process of Example 6.

EXAMPLE 6b

7-[3α-Butoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-hepten-1-ol

The named compound is prepared by substituting the compound of Example 1c in the process of Example 6.

EXAMPLE 6c

7-[3α-Propoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-hepten-1-ol

The named compound is prepared by substituting the compound of Example 1(a) in the process of Example 6.

EXAMPLE 6d

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-(2-propenoxy)-cyclopentyl]-5Z-hepten-1-ol

The procedure of Example 6 is repeated using the compound of Example 1(d) as the starting material to yield the named compound.

EXAMPLE 7

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3 α-methoxy-cyclopentyl]-5Z-heptenoic acid

40 mg (0.1047 mmol) of the compound of Example 1 were dissolved in a mixture of 0.31 mL of 0.5 N aqueous LiOH and 0.62 mL of THF in accordance with Reaction 2d of Scheme 2. After the reaction mixture was acidified with 10% aqueous citric acid and extracted with CH_2Cl_2. The organic portion was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by FCC using a 95 to 5 mixture of EtOAc and MeOH to yield 28.6 mg. (75% yield) of the named compound.

EXAMPLE 7a

7-[5αHydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-propoxy-cyclopentyl]-5Z-heptenoic acid

The named compound is prepared by substituting the compound of Example 1a in the procedure of Example 7.

EXAMPLE 7b

7-[3α-Ethoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenoic acid

The named compound is prepared by substituting the compound of Example 1b in the procedure of Example 7.

EXAMPLE 7c

7-[3α-Butoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenoic acid

The named compound is prepared by substituting the compound of Example 1c in the procedure of Example 7.

EXAMPLE 7d

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-(2-propenoxy)-cyclopentyl]-5Z-heptenoic acid

The named compound is prepared by substituting the compound of Example 1d in the procedure of Example 7.

EXAMPLE 8

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide

According to the procedures described for Example 4, the compound of Example 1 is reacted with NH_4Cl dissolved in NH_3 to yield the named compound.

EXAMPLE 8a

7-[3α-Ethoxy-5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenamide

In accordance with Example 8, 100 mg (0.252 mmol) of the compound of Example 1(b) is reacted with 135 mg (2.52

condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses.

Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20–35 ml.

The invention is further illustrated by the following non-limiting Examples.

EXAMPLE 1

Methyl 7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenoate

In accordance with Reaction 1b of Scheme 1, 300 mg. (0.815 mmols) of the 1-methylester of $PGF_{2\alpha}$ were dissolved in 1.0 mL of dimethylformamide (DMF). To this solution was added 150.5 mg. (0.649 mmol) of Ag_2O and 173.6 mg. (1.22 mmol) of methyliodide (MeI) and the resulting solution was stirred at 23° C. to obtain (8% yield) of the named compound in admixture with the 9-mono (4% yield), 15-mono and 11,15 bis (14% yield) methyl ethers of the, 1-methylester of $PGF_{2\alpha}$. (The compounds obtained in admixture with the named compound may also be referred to as the 5α-methoxy, 2β-(3α-methoxy-1E-octenyl) and 2β-(3α-methoxy-1E-octenyl)-3αmethoxy analogues of the named compound, respectively. The ethers were separated using high pressure liquid chromatography (HPLC) and eluting the admixture with a 1 to 1 mixture of hexane (hex) and ethylacetate (EtOAc) over a Whatman PARTISIL 10 PAK column.

EXAMPLE 1a

Methyl-7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3αpropoxycyclopentyl]-5Z-heptenoate.

The named compound may be prepared by substitution of n-propyliodide for methyl iodide in the procedure of Example 1.

EXAMPLE 1b

Methyl-7-[3αethoxy-5α-hydroxy-2β-(3α-1E-octenyl)-cyclopentyl]-5Z-heptenoate.

The named compound may be prepared by substitution of ethyliodide for methyl iodide in the procedure of Example 1.

EXAMPLE 1c

Methyl-7-[3α-Butoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenoate

The named compound may be prepared by substitution of n-butyliodide for methyl iodide in the procedure of Example 1.

EXAMPLE 1d

Methyl-7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α(2-propenoxy)-cyclopentyl]-5Z-heptenoate

The procedure of Example 1 is repeated using allyliodide in place of methyliodide to yield the named compound.

EXAMPLE 2

Isopropyl 7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenoate

The procedure of Example 1 was repeated except that the 1-isopropylester of $PGF_{2\alpha}$ was utilized as the reactant in place of the corresponding methylester to yield a reaction solution containing an admixture of mono and bis methyl ethers. The reaction solution was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was concentrated under vacuum, diluted with ethylether (Et_2O) and washed twice with water. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography (FCC) with an eluant of 1 to 1 hex/EtOAc to yield 120 mg. (59% yield) of the named compound and the 15-methyl ether analogue, thereof. 80% of the purified mixture was the named compound.

EXAMPLE 3

Isopropyl7-[5-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-propoxy-cyclopentyl]-5Z-heptenoate

20 mg. (0.050 mmol) of $PGF_{2\alpha}$ was combined with 47 mg (0.252 mmol of O-isopropyl N, N'-diisopropyl isourea in 1.0 mL of benzene and heated at 85° C. for 20 hours. The reaction mixture was concentrated in vacuo and the residue was purified by FCC using a 3 to 1 mixture of hexane and EtOAc to yield 16.3 mg. (74% yield) of the 11-isopropylester of $PGF_{2\alpha}$. The named compound may be prepared from said 11-isopropyl ester by substitution of propyliodide for methyliodide in the procedure of Example 2.

EXAMPLE 4

N-Isopropyl-7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide

In accordance with Reaction 2a of FIG. 2, 220 mg. (0.5759 mmol) of the compound of Example 1 were mixed with 549 mg (5.759 mmol) of isopropylamine hydrochloride in 6.0 mL of isopropylamine and heated in a sealed tube for 72 hours at 75° C. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed with water. The organic layer was treated as in Example 2 to yield 23.5 mg (10% yield) of the named compound.

EXAMPLE 4a

N,N-Dimethyl-7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide

The named compound is prepared in accordance with the procedure of Example 4 by using methylamine hydrochloride in methylamine.

EXAMPLE 4b

N-Isopropyl-7-(3α-ethoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenamide

The named compound is prepared by substituting the compound of Example 1b in the process of Example 4.

EXAMPLE 4c

N-Isopropyl-7-(5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-propoxy-cyclopentyl]-5Z-heptenamide

The named compound is prepared by substituting the compound of Example 1a in the process of Example 4.

Example 1b

Methyl-7-[3α-ethoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenoate.

The named compound may be prepared by substitution of ethyliodide for methyl iodide in the procedure of Example 1.

Example 1c

Methyl-7-[3α-Butoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl]-cyclopentyl]-5Z-heptenoate.

The named compound may be prepared by substitution of n-butyliodide for methyl iodide in the procedure of Example 1.

Example 1d

Methyl-7-[5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α (2-propenoxy)-cyclopentyl]-5Z-heptenoate.

The procedure of Example 1 is repeated using allyliodide in place of methyliodide to yield the named compound.

Example 2

Isopropyl 7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenoate

The procedure of Example 1 was repeated except that the 1-isopropylester of $PGF_{2\alpha}$ was utilized as the reactant in place of the corresponding methyl ester to yield a reaction solution containing an admixture of mono and bis methyl ethers. The reaction solution was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was concentrated under vacuum, diluted with ethylether (Et_2O) and washed twice with water. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The

residue was purified by flash column chromatography (FCC) with an eluant of 1 to 1 hex/EtOAc to yield 120 mg. (59% yield) of the named compound and the 15-methyl ether analogue, thereof. 80% of the purified mixture was the named compound.

Example 3

Isopropyl 7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-propoxy-cyclopentyl]-5Z-heptenoate

20 mg. (0.050 mmol) of $PGF_{2\alpha}$ was combined with 47 mg (0.252 mmol of O-isopropyl N, N'-diisopropyl isourea in 1.0 mL of benzene and heated at 85°C for 20 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by FCC using a 3 to 1 mixture of hexane and EtOAc to yield 16.3 mg. (74% yield) of the 11-isopropylester of $PGF_{2\alpha}$. The named compound may be prepared from said 11-isopropyl ester by substitution of propyliodide for methyliodide in the procedure of Example 2.

Example 4

N-Isopropyl-7-(5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide

In accordance with Reaction 2a of Figure 2, 220 mg. (0.5759 mmol) of the compound of Example 1 were mixed with 549 mg (5.759 mmol) of isopropylamine hydrochloride in 6.0 mL of isopropylamine and heated in a sealed tube for 72 hours at 75°C. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed with water. The organic layer was treated as in Example 2 to yield 23.5 mg (10% yield) of the named compound.

Example 4a

N,N-Dimethyl-7-(5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide

The named compound is prepared in accordance with the procedure of Example 4 by using methylamine hydrochloride in methylamine.

Example 4b

N-Isopropyl-7-(3α-ethoxy-5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenamide

The named compound is prepared by substituting the compound of Example 1b in the process of Example 4.

Example 4c

N-Isopropyl-7-(5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-propoxy-cyclopentyl]-5Z-heptenamide

The named compound is prepared by substituting the compound of Example 1a in the process of Example 4.

Example 4d

N,N-Dimethyl-7-(5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamide

Dimethylamine (~ 5 ml) was condensed in a tube containing 100 mg (0.1639 mmol) of the 5-t-butyldimethylsiloxy, 3-methoxy derivative of $PGF_{2\alpha}$, methylester dissolved in 6.0 mL of CH_3OH. The resultant solution was stirred in a sealed glass tube for 48 hours and concentrated *in vacuo*. The residue diluted with THF (1.0 mL) and treated with Bu_4NF (0.26 mL of a 1.0M solution, 0.262 mmol) at

23°C. After 16 hours, the reaction was diluted with Et_2O and washedwith H_2O. The organic portion was dried ($MgSO_4$), filtered and concentrated *in vacuo*. FCC (100% EtOAc followed by 9:1 CH_2Cl_2/MeOH) gave 24.2 mg. (39%) of the product.

Example 5

N-Isopropyl-7-(5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamine

In accordance with Reaction 2b of Figure 2, 75 mg of the compound of Example 4, dissolved in 2.0 mL of tetrahydrofuran (THF) were treated with 34.6 mg. (0.9165. mmol) of lithium aluminumhydride (LAH) at 23°C. After 24 hours, the reaction mixture was quenched with 2.0 N NaOH and extracted with EtOAc. The organic layer was dried over anhydrous MgSO4, filtered and concentrated under vacuum. The residue was purified with FCC using a 6:1:0.1 mixture of CH_2Cl_2/MeOH/NH4OH to yield 19.0 mg. (26% yield) of the named compound.

Example 5a

N,N-Dimethyl-7-(5α-hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-heptenamine

The named compound is prepared by substitution of the compound of Example 4a in the procedure of Example 5.

Example 6

7-(5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5Z-hepten-1-ol

In accordance with Reaction 2c of Figure 2, 20.2 mg (0.0529 mmol) of the compound of Example 1 were dissolved in 1.5 mL of Et_2O and treated with 2.3 mg (0.105 mmol) of $LiBH_4$ to yield a

mmol) of NH_4Cl dissolved in 5 mL of NH_3 to give the named compound in 69% yield.

EXAMPLE 8b

7-[5α-Hydroxy-2β-(3α-hydroxy-1-E-octenyl)-3α-propoxy-cyclopentyl]-5Z-heptenamide

In accordance with Example 8, 52 mg (0.127 mmol) of the compound of Example 1(a) is reacted with 68 mg (1.27 mmol) of NH_4Cl dissolved in 4.5 mL of NH_3 to give the named compound in 86% yield.

EXAMPLE 9

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-1-pivaloyloxy 5Z-heptene

The 1-t-butyldimethylsilyl ester of 3-methoxy $PGP_{2\alpha}$ and 5.2 mg (0.239 mmol) of $LiBH_4$ was dissolved in 1.0 mL of ethylether and stirred for 16 hours at 23° C. The reaction mixture was quenched with 2.0 N aqueous NaOH and extracted with CH_2Cl_2. The organic portion was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was dissolved in 0.5 mL of pyridine and cooled to 0° C. 17.7 uL(0.143 mmol) of trimethylacetyl chloride were added and after 24 hours the reaction was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine and dried over anhydrous $MgSO_4$. The dried product was filtered and concentrated under vacuum before purifying by use of FCC and a 1 to 1 mixture of hexane and EtOAc to yield 15.9 mg (31% yield of the named compound).

EXAMPLE 10

7-[3α,5α-Dihydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-1-methoxy-5Z-heptene

In accordance with Reaction 2e of Scheme 2, a solution of the compound of Example 6 and 0.46 mL 2, 6-di-t-butylpyridine (2.058 mmol) in 2.0 mL CH_2Cl_2 was treated with methyl triflate (194 ul, 1.715 mmol) and stirred for 48 hours at 23° C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic portion was died over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was diluted with 20 mL of THF and 1.4 mL of a 1.0M solution of Bu_4NF in THF. After 16 hours, the reaction was diluted with EtOAc and washed with H_2O. The organic portion was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Treating by FCC with 1:1 hex/EtOAc gave 66.1 mg (53% yield) of the named compound.

EXAMPLE 11

1-Acetoxy-7-[3α-5α-Dihydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-heptene

1-Acetoxy-7-[3 α, 5α-t-butyldimethylsiloxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-heptene is reacted with Bu_4NF in THF at room temperature to yield the named compound.

EXAMPLE 12

Methyl 7-[3α-Hydroxy-2β-(3αhydroxy-1E-octenyl)-5α-methoxy-cyclopentyl]-5Z-heptenoate

The named compound is prepared in accordance with the procedure of Example 1.

EXAMPLE 12a

7-[3α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-5α-(methoxy-cyclopentyl]-5Z-heptenoic acid

The named compound is prepared by reacting the compound of Example 12 in accordance with the process of Example 7.

EXAMPLE 12b

7-[3α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-5α-(methoxy-cyclopentyl]-5Z-hepten-1-ol

The named compound is prepared by reacting the 1-t-butyl dimethylsiloxy ester of the compound of Example 12(a) in accordance with the process of Example 6.

EXAMPLE 13

7-[3α-5α-Dihydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-hepten-1-ol

The 15-monomethyl ether of Example 1 is reacted in accordance with the process of Example 6 to yield the named compound.

EXAMPLE 13a

7-[3α-5α-Dihydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-heptenoic acid

The 15-monomethyl ester of Example 1 is reacted in accordance with the process of Example 7 to yield the named compound.

EXAMPLE 13b

Isopropyl-7-[3α-5α-Dihydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-heptenamide

The 15-monomethyl ester of Example 1 is reacted in accordance with the process of Example 4 to yield the named compound.

EXAMPLE 13c

7-[3α-5α-Dihydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-heptenamide

The 15-monomethyl ester of Example 1 is reacted in accordance with the process of Example 8 to yield the named compound.

EXAMPLE 14

Methyl-7-[3α-5α-Dihydroxy-2β-(3α-ethoxy-1E-octenyl)-cyclopentyl]-5Z-heptenoate

The named compound is prepared in accordance with the process of Example 1 by replacing methyliodide with ethyl iodide.

EXAMPLE 14a

7-[3α-5α-Dihydroxy-2β-(3α-ethoxy-1E-octenyl)-cyclopentyl]-5Z-heptenoic acid

The named compound is prepared by reacting the compound of Example 14 in accordance with the process of Example 7.

EXAMPLE 14b

N-Isopropyl-7-[3α-5α-Dihydroxy-2β-(3α-ethoxy-1E-octenyl)-cyclopentyl]-5Z-heptenamide

The named compound is prepared by reacting the compound of Example 14 in accordance with the process of Example 4.

Example 8a

7-[3α-Ethoxy-5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-cyclopentyl]-5Z-heptenamide

In accordance with Example 8, 100 mg (0.252 mmol) of the compound of Example 1(b) is reacted with 135 mg (2.52 mmol) of NH_4Cl dissolved in 5 mL of NH_3 to give the named compound in 69% yield.

Example 8b

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-propoxy-cyclopentyl]-5Z-heptenamide

In accordance with Example 8, 52 mg (0.127 mmol) of the compound of Example 1(a) is reacted with 68 mg (1.27 mmol) of NH_4Cl dissolved in 4.5 mL of NH_3 to give the named compound in 86% yield.

Example 9

7-[5α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-1-pivaloyloxy 5Z-heptene

The 1-t-butyldimethylsilyl ester of 3-methoxy $PGF_{2\alpha}$ and 5.2 mg (0.239 mmol) of $LiBH_4$ was dissolved in 1.0 mL of ethylether and stirred for 16 hours at 23°C. The reaction mixture was quenched with 2.0 N aqueous NaOH and extracted with CH_2Cl_2. The organic portion was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was dissolved in 0.5 mL of pyridine and cooled to 0°C. 17.7 uL(0.143 mmol) of trimethylacetyl chloride were added and after 24 hours the reaction was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine and dried over anhydrous $MgSO_4$. The dried product was filtered and concentrated under vacuum before purifying by use of FCC and a 1 to 1 mixture of hexane and EtOAc to yield 15.9 mg (31% yield of the named compound).

Example 12

Methyl 7-[3α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-5α-methoxy-cyclopentyl]-5Z-heptenoate

The named compound is prepared in accordance with the procedure of Example 1.

Example 12a

7-[3α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-5α-methoxy-cyclopentyl]-5Z-heptenoic acid

The named compound is prepared by reacting the compound of Example 12 in accordance with the process of Example 7.

Example 12b

7-[3α-Hydroxy-2β-(3α-hydroxy-1E-octenyl)-5α-methoxy-cyclopentyl]-5Z-hepten-1-ol

The named compound is prepared by reacting the 1-t-butyl dimethylsiloxy ester of the compound of Example 12(a) in accordance with the process of Example 6.

Example 13

7-[3α-5α-Dihydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-hepten-1-ol

The 15-monomethyl ether of Example 1 is reacted in accordance with the process of Example 6 to yield the named compound.

EXAMPLE 18b

7-[5α-Hydroxy-2β-(3α-Hydroxy-1E-octenyl)-3α-methoxy-cyclopentyl]-5E-hepten-1-ol

The named compound is prepared by substituting the compound of Example 18 in the process of Example 6.

EXAMPLE 19

Methyl-7-[3α-methoxy-5α-hydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-heptenoate

The named compound is isolated from the reaction product of Example 1.

EXAMPLE 19a

7-[3α-methoxy-5α-hydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-heptenoic acid

The named compound is prepared by substituting the dimethylether of Example 19 in the process of Example 7.

EXAMPLE 19b

7-[3α-methoxy-5α-hydroxy-2β-(3α-methoxy-1E-octenyl-cyclopentyl]-5Z-hepten-1-ol

The named compound is prepared by substituting the dimethylether of Example 19 in the process of Example 6.

EXAMPLE 20

Effects on Intraocular Pressure

The effects of certain of the above examples on intraocular pressure are provided in the following Table 1. The compounds were prepared at the said concentrations in a vehicle comprising 0.1% polysorbate 80 and 10 mM TRIS base. Dogs were treated by administering 25 ul to the ocular surface, the contralateral eye received vehicle as a control. Intraocular pressure was measured by application pneumatonometry. Dog intraocular pressure was measured immediately before drug administration and at 4 hours thereafter.

The examples which show excellent IOP-lowering effect include Examples 1, 1a, 1b, 6 and 6a wherein the 11 position is substituted with a lower alkyl ether, i.e. a C_1 to C_3 alkyl ether and the 1-position is a lower alkyl ester, e.g. a methyl ester, or an alcohol group. Furthermore, a comparison of Example 1 and 18 shows that the 5-trans or 5-cis isomers are substantially similar in their IOP-lowering effect. Finally, the 9 and 15-substituted lower alkyl ether derivatives wherein the 1-position is substituted with a lower alkyl ester group are also very effective in lowering IOP. (Compare Examples 12 and the 15-monoester of Example 1.) In contrast, various derivatives wherein the 11-position is substituted with a lower alkyl ether group and the 1-position is an acid or an amino group showing lower effect in lowering IOP at a concentration of 0.1%. (See Examples 4a, 4b, 4c, 5, 7d, 18a, 19a and 19b.) However, it is believed that higher concentrations would have greater effect in lowering IOP.

In Table 1, hyperemia is measured by visual estimation. Slight hyperemia would be given a value between 0 and 0.5; moderate hyperemia would be given a value from 0.5 to 1.0 and severe hyperemia would be given a value of greater than 1.0. Miosis would be evaluated as 0 (nothing), slight (slite) or pinpoint (pin), i.e. the pupil would be the size of a pinpoint.

TABLE 1

EXAMPLE	DOG IOP	HYPEREMIA/ MIOSIS
1	0.01/+3.0	0.03/0
	0.1%/−6.2	0.50/pin
6	0.01/−1.6	0.08/0
	0.1%/−5.7	0.75/pin
17a	0.1%/−1.3	0.03/slite
17	0.1%/−2.5	0.82/pin
9	0.1%/−2.5	0.17/slite
18	0.01/0	0.08/slite
	0.1%/−6.3	0.03/slite
18a	0.1%/0.0	0/0
18b	0.1%/−3.0	0.03/slite
1b	0.1%/−5.2	0.44/pin
7b	0.1%/−3.9	0.75/pin
6a	0.1%/−6.5	0.03/pin
	01%/0.0	
8	0.1%/−3.3	0.56/pin
4a	0.1%/0.0	0.33/slite
1d	0.1%/−3.8	0.66/pin
6d	0.1%/−2.3	0.58/pin
7d	0.1%/0.0	0.31/pin
19	0.1%/−2.4	0.75/pin
19a	0.1%/0.0	0.04/0
19b	0.1%/0.0	0/slite
12	0.01/−3.3	0/slite
	0.1%/−7.8	0.53/pin
12a	0.1%/−2.8	0.25/slite
12b	0.1%/−4.2	0/slite
5	0.1%/0.0	0.08/0
6c	0.1%/−2.0	0.29/slite
7a	0.1%/−3.9	0.54/pin
	0.01/0	0.62/slite
1a	0.1%/−7.6	0.83/pin
	0.01/0	0.29/slite
1	0.1%/−7.8	0.89/pin
(15-mono ester)	0.01/−2.0	0.83/pin
	0.1%/−4.5	1.34/pin
11	0.1%/−2.9	0.42/slite
10	0.1%/−1.8	0/0
8a	0.1%/0	0.29/pin
	0.1%/−2.9	0.21/pin
4b	0.1%/0	0.08/slite
13b	0.1%/−3.9	0.5/pin
14	0.1%/−4.5	0.50/pin
1c	0.1%/−4.4	1.17/pin
6b		
7c	0.1%/−1.6	0.70/0
4c	0.1%/0	0/0
8b	0.1%/−3.8	0.79/pin
2a	0.1%/−1.8	0.47/pin
13c	0.1%/−3.2	0.59/pin
	0.01%/−4.0	0.44/pin
14d	0.1%/−2.7	0.46/pin
	0.1%/−5.1	0.81/pin
2	0.1%/−4.2	0.56/pin
16a	0.1%/−3.8	ND/pin
16b	0.1%/−4.4	0.47/pin

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent from one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same results. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

Example 19a

7-[3α-methoxy-5α-hydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-heptenoic acid

The named compound is prepared by substituting the dimethylether of Example 19 in the process of Example 7.

Example 19b

7-[3α-methoxy-5α-hydroxy-2β-(3α-methoxy-1E-octenyl)-cyclopentyl]-5Z-hepten-1-ol

The named compound is prepared by substituting the dimethylether of Example 19 in the process of Example 6.

Example 20
EFFECTS ON INTRAOCULAR PRESSURE

The effects of certain of the above examples on intraocular pressure are provided in the following Table 1. The compounds were prepared at the said concentrations in a vehicle comprising 0.1% polysorbate 80 and 10 mM TRIS base. Dogs were treated by administering 25 ul to the ocular surface, the contralateral eye received vehicle as a control. Intraocular pressure was measured by application pneumatonometry. Dog intraocular pressure was measured immediately before drug administration and at 4 hours thereafter.

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ester group are also very effective in lowering IOP. (Compare Examples 12 and the 15-monoester of Example 1.) In contrast, various derivatives wherein the 11-position is substituted with a lower alkyl ether group and the 1-position is an acid or an amino group showing lower effect in lowering IOP at a concentration of 0.1%. (See Examples 4a, 4b, 4c, 5, 7d, 18a, 19a and 19b.) However, it is believed that higher concentrations would have greater effect in lowering IOP.

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TABLE 1

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	0.1%/-5.7	0.75/pin
17a	0.1%/-1.3	0.03/slite
17	0.1%/-2.5	0.82/pin
9	0.1%/-2.5	0.17/slite
18	0.01/0	0.08/slite
	0.1%/-6.3	0.03/slite
18a	0.1%/0.0	0/0
18b	0.1%/-3.0	0.03/slite
1b	0.1%/-5.2	0.44/pin
7b	0.1%/-3.9	0.75/pin
6a	0.1%/-6.5	0.03/pin
	01%/0.0	